THE PHARMACOLOGIC MANAGEMENT OF CHRONIC HEART FAILURE (HF)

Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel (PBM-MAP)

Guideline Summary

EXECUTIVE SUMMARY

- All patients with HF should have an evaluation of left ventricular function. A diagnosis of HF due to systolic dysfunction can be made by a 2-dimensional echocardiogram with Doppler flow studies. In general, patients with a left ventricular ejection fraction (LVEF) of $\leq$ 40% are defined as having systolic dysfunction. Other tests (e.g., radionuclide ventriculography) may be used to determine left ventricular systolic function, non-invasively.
- Nonpharmacologic therapy includes abstaining from alcohol and tobacco, limiting dietary sodium, reducing weight if appropriate, and participating in exercise training programs.
- Pharmacologic treatment has been shown to improve symptoms, increase functional capacity, improve quality of life, slow disease progression, decrease need for hospitalization, and prolong survival.
- Increase pharmacologic therapy as tolerated in an effort to achieve target doses.
- Schedule regular follow-up and assess for change in functional status.
- Cardiology referral may be requested at any point in the care of the patient. Some facilities may have interdisciplinary HF disease management clinics to provide continuity of care for patients with HF.

KEY POINTS FOR PHARMACOLOGIC MANAGEMENT OF HF (REFER TO BOX NUMBER IN ALGORITHM)

- Consider anticoagulation if atrial fibrillation or history of thromboembolism (Box 4,5).
- Early post-myocardial infarction (MI) treatment with an ACEI in patients with left ventricular systolic dysfunction may prevent future development of HF and improve overall survival (Box 10).
- A diuretic should be used in the treatment of patients with symptoms or signs of fluid overload (Box 8,9).
- All patients with significantly reduced left ventricular function, including asymptomatic patients, should be treated with an ACEI unless contraindicated or not tolerated (Box 10).
- A ß-adrenergic blocker should be used in conjunction with an ACEI in all patients with stable NYHA class II or III HF, unless contraindicated or not tolerated (Box 15, 16).
- Digoxin should be used in patients with moderate to severe HF whose symptoms persist despite treatment with an ACEI, a ß-blocker, and a diuretic (Box 18).
- Hydralazine and isosorbide dinitrate (HYD/ISDN) should be considered in patients with contraindications to or who cannot tolerate an ACEI. An angiotensin II receptor antagonist (AIIRA) is an additional alternative for patients who cannot tolerate an ACEI due to cough (Box 11, 12).
- Low dose spironolactone should be considered in patients with recent NYHA class IV HF and current class III or IV symptoms, unless contraindications exist (Box 20, 21).

VA access to full guideline: http://www.oqp.med.va.gov/cpg
DoD access to full guideline: http://www.cs.amedd.army.mil/Qmo

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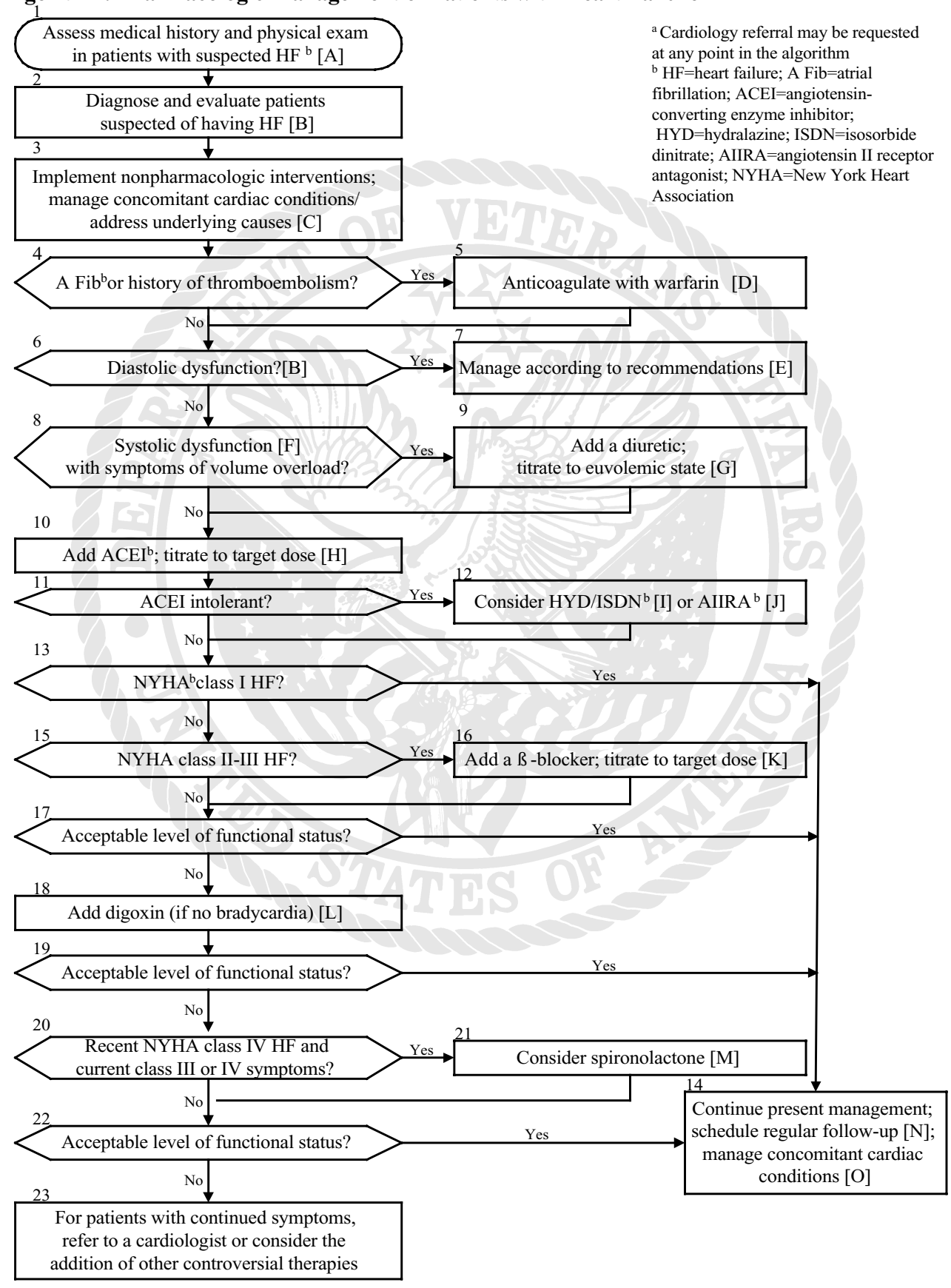
Algorithm: Pharmacologic Management of Patients with Heart Failure [a]



[a] Cardiology referral may be requested at any point in the algorithm

[b] HF=heart failure; A Fib=atrial fibrillation; ACEI=angiotensin-converting enzyme inhibitor; HYD=hydralazine; ISDN=isosorbide dinitrate; AIIRA=angiotensin II receptor antagonist; NYHA=New York Heart Association

(Annotation A)	
Symptoms of HF	**Signs of HF**
Shortness of breath (SOB) Cough Orthopnea Paroxysmal nocturnal dyspnea (PND) Dyspnea on exertion (DOE) Edema Fatigue Weight gain	Tachycardia Increasing weight Jugular venous distention (JVD) or hepatojugular reflux Presence of S_3 (third heart sound) Laterally displaced apical impulse Pulmonary crackles or wheezes Hepatomegaly Peripheral edema

Recommended Tests to Assist in the Diagnosis of HF (Annotation B)
Creatinine (Cr), Blood urea nitrogen (BUN), Serum electrolytes, Urinalysis, Albumin, Bilirubin, Prothrombin time, Complete blood count (CBC), Thyroid stimulating hormone (TSH) Electrocardiogram, Chest radiography

NYHA Functional Classification (Annotation B)
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or angina.
Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class III: Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or angina.
Class IV: Unable to carry on any physical activity without discomfort. Symptoms are present at rest. With any physical activity, symptoms increase.

Adapted from the Criteria Committee of the American Heart Association. 1994 revisions to the classification of functional capacity and objective assessment f patients with disease of the heart. Circulation 1994;90:644-5.

Recommendations for Nonpharmacologic Therapy (Annotation C)

To decrease risk of new cardiac injury:

- Weight loss if body mass index $\geq$ 30kg/m^2 (obesity) after adjustment for fluid retention
- Smoking cessation [refer to VHA/DoD Clinical Practice Guideline to Promote Tobacco Use Cessation in the Primary Care Setting, "Tobacco Use Cessation" May 1999;101(93):1633 at http://vaww.oqp.med.va.gov]
- Alcohol consumption should be discouraged
- Manage comorbidities to reduce risk of further myocardial damage [e.g., HTN, dyslipidemia, diabetes mellitus (DM)] (refer to http://www.vapbm.org or http://vaww.pbm.med.va.gov for documents containing treatment recommendations for these conditions)

To maintain fluid balance:

- Restrict daily sodium intake to 2 to 3 grams per day (1 gram sodium = 2.5 grams salt)
- Daily weight measurements to assess for fluid retention
- Fluid restriction is generally needed only to correct a clinically important hyponatremia rather than being a generalized treatment for HF; however, high fluid intake (e.g., > 3 liters per day) should be discouraged

Moderate exercise (e.g., walking or cycling) to improve physical conditioning in stable NYHA Class I-III HF; patients should be referred to a specialist if the clinician is not comfortable designing an exercise program for the patient with HF.

SPECIFIC RECOMMENDATIONS FOR MEDICATIONS USED IN THE TREATMENT OF HF

ACEI (Annotation H)	Initial dose (Target doses[e])	Comments/Cautions
Captopril[f]	12.5 mg tid (50 mg tid)	• Start with lower or less frequent doses in patients with renal insufficiency
Enalapril	2.5 mg bid (10mg bid)	• CrCl < 30 mL/min, initial dose 2.5mg qd
Fosinopril	10 mg qd (20-40 mg qd)	• Start with 5mg qd if moderate to severe renal failure
Lisinopril	5 mg qd (20-40 mg qd)	• CrCl < 30 mL/min, initial dose 2.5mg qd
		Contraindications to all ACEI • History of angioedema or other documented hypersensitivity to an ACEI; Bilateral renal artery stenosis or renal artery stenosis in a solitary kidney; Symptomatic hypotension; Pregnancy; Serum potassium > 5.5 mEq/L that cannot be reduced
Drug (Annotation I)	**Dose Range**	**Comments/Cautions**
Hydralazine	initial= 75 mg/d (3-4 divided doses); range= 75-300 mg/d (3-4 divided doses); (ave. dose V-HeFT II 200 mg/d[g])	• Monitor adverse effects: dizziness, headache, lupus-like syndrome, nausea, tachycardia, postural hypotension • Advise patient to take with food
Isosorbide dinitrate	initial= 30 mg/d (3 divided doses); range=30-160mg/d (3 divided doses); (ave. dose V-HeFT II 100 mg/d[g])	• Monitor adverse effects: flushing, headache, postural hypotension, rash • May cause an increase in ocular pressure; caution with presence of glaucoma
AIIRA (Annotation J)	**Dose Range**	**Comments/Cautions**
Candesartan 4, 8, 16, 32mg tablets	8-32mg divided qd-bid	• All AIIRAs are contraindicated in 2nd and 3rd trimesters pregnancy due to potential neonatal/fetal morbidity and death • Use AIIRAs with caution in patients with renal artery stenosis • Initiate losartan at 25mg and use telmisartan with caution in patients with hepatic impairment • An AIIRA should be used with caution, if at all, in patients who have previously experienced angioedema with an ACEI
Irbesartan 75, 150, 300mg tablets	75-300mg qd	
Losartan 25, 50mg tablets	25-100mg divided qd-bid	
Telmisartan 40, 80mg tablets	40-80mg qd	
Valsartan 80, 160mg capsules	80-320mg qd	

β-Blocker (Annotation K)	Dose Range	Comments/Cautions
Cardioselective **Metoprolol** **Metoprolol XL** **Bisoprolol** **α & β antagonist** **Carvedilol**[h]	Initial 6.25 mg (see comments) qd/bid; titrate slowly to 12.5-25 mg bid to target 50-75mg bid Initial 12.5-25mg qd; double dose every 2 wks to target dose 200mg qd (or as tolerated) Initial 1.25mg qd; increase by 1.25mg q wk until 5mg qd, then increase by 2.5mg q 4 wks to target 10mg qd Initial 3.125 mg bid, range 6.25-25 mg bid (patients ‡ 85 kg may be titrated to 50mg bid); titrate at minimum of q 2 wks to target 25-50mg mg bid	• Cardioselectivity is dose related • Caution should be used when using β-adrenergic blockers in patients with systolic dysfunction • Low initial doses should be implemented • Use slow gradual increases in the dosage • Effects are generally seen in 3-12 months • Low dosages of metoprolol immediate-release are not commercially available, although various methods of titration have been used;[i] low dose metoprolol XL is available for titration; consult with pharmacy for options • Do not use in patients with bronchospastic disease, symptomatic bradycardia, or advanced heart block without a pacemaker • Should not be abruptly discontinued • Carvedilol should be given with food to reduce the incidence of orthostatic hypotension; consider separating the ACEI, adjusting dose of diuretic, or temporary ACEI dose reduction if dizziness occurs

Drug	Dose Range	Comments/Cautions
Digoxin **(Annotation L)**	Initial = 0.125 mg qd Range = 0.0625-0.375 mg qd	Trough serum digoxin levels should be monitored if: • HF worsens or renal function deteriorates • Signs of toxicity develop (e.g., confusion, nausea, vomiting, abdominal pain, diarrhea, anorexia, fatigue, arrhythmias, visual disturbances) • Dose adjustments are made • Medications added that affect digoxin concentration (e.g., quinidine, verapamil, amiodarone, antibiotics, anticholinergics)
Spironolactone **(Annotation M)**	Initial = 25mg qd Range = 25mg qod-50mg qd	• Potential side effects include gastrointestinal, gynecomastia, hyperkalemia, menstrual irregularities • Hyperkalemia occurs more frequently in patients on K+ supplements and patients with renal insufficiency • K+ supplements should be avoided with spironolactone unless hypokalemia develops • Use with caution in patients with renal insufficiency • Schedule follow-up electrolytes (check K+ q 4 wks for first 3 months, then q 3 months for first yr and then q 6 months) and renal function after initiation and dose adjustments • Use with caution in patients receiving ACEIs due to the potential for hyperkalemia

Bold = National Formulary item

Adapted from Hebel SK, ed. Drug Facts and Comparisons, St. Louis, Missouri: Facts and Comparisons Inc., 1999; Heart failure: Management of patients with left ventricular systolic dysfunction. Clinical Practice Guideline, No. 11. Rockville, MD. U.S. Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research. AHCPR Publication No. 94-0613; McEvoy GK, ed.

American Hospital Formulary Service Drug Information, Bethesda, MD:American Society of Health-System Pharmacists, Inc., 1999.

[a] Higher doses have been effective and tolerated

[b] Unless patients have persistent hypokalemia or are being treated with low dose spironolactone for severe HF (Annotation M), potassium-sparing diuretics should not be used in combination with ACEI (Appendix 1)

[c] The brand names of metolazone are not bioequivalent, therefore doses vary

[d] Intermittent use recommended once the response of the patient is stabilized

[e] Target doses for HF were derived from major trials and AHCPR guidelines. Excluding captopril and enalapril, doses for HF reflect doses used to increase exercise tolerance in HF patients

[f] One hour before meals, on an empty stomach

[g] Cohn JN, Johnson G, Ziesche S et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303-10.

[h] Carvedilol is FDA approved for the treatment of mild-moderate HF stabilized on standard therapy

[i] Eichhorn EJ, Bristow MR. Practical guidelines for initiation of beta-adrenergic blockade in patients with chronic heart failure. Am J Cardiol 1997;79:794-8

Patient Education and Follow-Up (Annotation N)

Proper education of patients and their family is imperative so that they may have an understanding of the cause of HF, prognosis, therapy, dietary restrictions, activity, adherence, and the signs and symptoms of recurrent HF.

Nonpharmacologic therapy including abstaining from alcohol and tobacco, limiting dietary sodium, reducing weight if appropriate, and participating in exercise training programs should be discussed with the patient.

Inquiry should be made as to the patient's adherence to the medication regimen and nonpharmacologic measures, and adverse effects to therapy.

Concomitant cardiac conditions should be managed (Annotation C, O).

Patients should be scheduled for regular follow-up and assessed for change in functional status.

Some facilities may have interdisciplinary HF disease management clinics to provide continuity of care for patients with HF.